REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The 35 U.S.C. §112 Rejection

Claims 11-17, 19-21, 23, 24, 27-30, 40-45 and 53-56 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claims 11 and 14 have been amended to recite a method of using the gene delivery system of the instant invention to genetically modifiy $CD40^+$ immune cells. The gene delivery system of the instant invention can both mediate gene transfer to $CD40^+$ immune cells and cause maturation of $CD40^+$ immune cells, and the $CD40^+$ immune cells can be modified *ex vivo* or by intradermal injection.

The present invention discloses enhanced gene transfer to $CD40^+$ cells by retargeting the adenovirus to CD40. CD40-targeted virus demonstrated both dramatic and quantitative improvements in gene transfer compared to untargeted virus (Examples 1, 3-4). The claimed gene delivery systems also induce maturation of $CD40^+$ cells as manifested by phenotypic and functional criteria (Examples 1, 3). In these examples, the CD40-targeted viruses were administered *ex vivo* or *in situ* to cutaneous dendritic cells

Therefore, Applicants submit that the scopes of claims 11 and 14 are commensurate with the enablement provided in the specification. Accordingly, Applicants respectfully request that the rejection of claims 11, 13, 14, and 16 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 17, 20-21, 24, 29-30, 40, 42, 43, 45, 53 and 55 are drawn to methods of using the CD40-targeted adenoviral vectors of the instant invention to enhance the vaccination potential of dendritic cells. As discussed above, the CD40-targeted adenoviral vectors of the instant invention mediate both gene transfer to and cause maturation of $CD40^+$ dendritic cells. Consequently, dendritic cells modified by the CD40-targeted adenoviral vectors of the instant invention have increased vaccination potential.

The present specification employs a HPV-induced tumor model and an adenovirus vector, AdE7, that expresses a functionally mutated gene for the E7 antigen of HPV to establish the immunization efficacy of adenoviral modified dendritic cells. The advantage of CD40-targeting of Ad in a vaccination context was demonstrated in a dose response curve comparing untargeted (AdE7) and CD40-targeted AdE7 (40AdE7) vectors (Example 3). At a dose of 12,000 dendritic cells, for example, tumors developed in animals vaccinated with dendritic cells transduced by untargeted AdE7 but not in animals immunized with CD40AdE7 (Figure 13). Of note, among the tumors that did develop in mice in the lower dosage classes of E7 modified dendritic cells, the kinetics of tumor growth was slower than that in unvaccinated mice.

These findings indicate that features of CD40-targeted Ad, namely increased gene transfer and induced maturation of dendritic cells, confer an increased vaccination potential to the treated dendritic cells.

In view of the above remarks, Applicants submit that the claims on the methods of enhancing the vaccination potential of dendritic cells have reasonable correlation to the scope of the enablement provided by the specification. Accordingly, Applicants respectfully request that the rejection of claims 17, 20-21, 24, 29-30, 40, 42, 43, 45, 53 and 55 under 35 U.S.C. §112, first paragraph, be withdrawn.

Double Patenting

Claims 1, 3-10, 25, 26, 31, 33-37 and 46-50 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent 6,284,742. The rejection is respectfully traversed.

Claims 31 and 46 are drawn to genetically modified adenoviruses having a fiber protein comprising a CD40 ligand, wherein the fiber shaft of the fiber protein is replaced by bacteriophage T4 fibritin protein. Example 7 of the instant specification teaches the making of these modified adenoviruses. A fiber chimera comprising a CD40L globular domain and a bacteriophage fibritin which replaces the natural fiber shaft was disclosed therein.

In contrast, claims 1-6 of U.S. Patent 6,284,742 only claim a gene delivery system comprising an adenovirus and a bispecific antibody that targets

the adenovirus to CD40. U.S. Patent 6,284,742 did not teach or suggest a genetically modified adenovirus having a fiber protein comprising CD40 ligand and bacteriophage T4 fibritin protein as claimed herein. Hence, claims 31, 34-37 and 46-50 of the instant application are not co-extensive with claims 1-6 of U.S. Patent 6,284,742. Accordingly, Applicants respectfully request that the double patenting rejection of claims 31, 34-37 and 46-50 be withdrawn.

Claims 1, 3-10, 25, 26, 31, 33-39 and 46-52 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent 6,284,742 in view of **Krul** et al. The rejection is respectfully traversed.

Claim 31 and U.S. Patent 6,284,742 have been discussed above. **Krul** et al. taught recombinant vaccine expressing HPV type 16 E6 and E7 proteins. The Examiner contends that the present application differs from the cited patent in that the cited patent did not teach HPV type 16 E7 protein and **Krul** et al. provided the HPV teaching. Applicants respectfully disagree.

Applicants submit that the present application differs from the cited patent not only in the teaching of HPV type 16 E7 protein. Claim 31 is drawn to a genetically modified adenovirus having a fiber protein comprising CD40 ligand and bacteriophage T4 fibritin protein. In contrast, U.S. Patent 6,284,742 did not teach or suggest a genetically modified adenovirus having a fiber protein comprising CD40 ligand and bacteriophage T4 fibritin protein as claimed herein. Therefore, combining U.S. Patent 6,284,742 and **Krul** et al.

would not lead a person having ordinary skill in this art to produce Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the double patenting rejection of claims 31, 34-39 and 46-52 be withdrawn.

This is intended to be a complete response to the Final Office Action mailed October 2, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Dec 12, 2002

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391
badler1@houston.rr.com

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 11 has been amended as follows:

11. (thrice amended) A method for genetically manipulating $CD40^+$ immune cells ~~in an individual~~, comprising the step of:

administering the gene delivery system of claim 1 to said immune cells ~~individual~~, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

Claim 12 has been amended as follows:

12. (amended) The method of claim 11, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 14 has been amended as follows:

14. (thrice amended) A method for genetically manipulating $CD40^+$ immune cells ~~in an individual~~, comprising the step of:

administering the gene delivery system of claim 6 to said immune cells ~~individual~~, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

Claim 15 has been amended as follows:

15. (amended) The method of claim 14, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 17 has been amended as follows:

17. (thrice amended) A method for enhancing the vaccination potential of dendritic cells ~~based vaccination in an individual~~, comprising the step of:

administering the gene delivery system of claim 1 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases vaccination efficacy of CD40~~$^+$ dendritic cells ~~in said individual~~.

Claim 19 has been amended as follows:

19. (amended) The method of claim 17, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 21 has been amended as follows:

21. (thrice amended) A method for enhancing the vaccination potential of dendritic cells ~~based vaccination in an individual~~, comprising the step of:

administering the gene delivery system of claim 1 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases vaccination efficacy of CD40~~* dendritic cells ~~in said individual~~.

Claim 23 has been amended as follows:

23. (amended) The method of claim 21, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 31 has been amended as follows:

31. (twice amended) A recombinant adenoviral vector, comprising:

a genetically modified adenovirus having a fiber protein comprising CD40 ligand, wherein the fiber shaft of said fiber protein is replaced by bacteriophage T4 fibritin protein and said CD40 ligand targets said vector to CD40.

Claim 40 has been amended as follows:

40. (thrice amended) A method for enhancing the vaccination potential of dendritic cells ~~based vaccination in an individual~~, comprising the step of:

administering the gene delivery system of claim 34 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases vaccination efficacy of~~ $CD40^+$ dendritic cells ~~in said individual~~.

Claim 41 has been amended as follows:

41. (amended) The method of claim 40, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 43 has been amended as follows:

43. (thrice amended) A method for enhancing the vaccination potential of dendritic cells ~~based~~ vaccination ~~in an individual~~, comprising the step of:

administering the gene delivery system of claim 34 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases~~ vaccination efficacy of $CD40^+$ dendritic cells in said individual

Claim 44 has been amended as follows:

44. (amended) The method of claim 43, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 53 has been amended as follows:

53. (thrice amended) A method for enhancing the vaccination ~~potential of~~ dendritic cells ~~based vaccination in an individual~~, comprising the step of:

administering the gene delivery system of claim 47 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases vaccination efficacy of CD40~~* dendritic cells ~~in said individual~~.

Claim 54 has been amended as follows:

54. (amended) The method of claim 53, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.

Claim 55 has been amended as follows:

55. (thrice amended) A method for enhancing the vaccination potential of dendritic cells ~~based vaccination in an individual~~, comprising the step of:

administering the gene delivery system of claim 51 to said dendritic cells ~~individual~~, wherein said gene delivery system mediates gene transduction and increases the vaccination potential of said ~~increases vaccination efficacy of CD40$^+$~~ dendritic cells ~~in said individual~~.

Claim 56 has been amended as follows:

56. (amended) The method of claim 55, wherein said cells are obtained from individual who has a disease selected from the group consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease.